

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
5 December 2002 (05.12.2002)

PCT  
(10) International Publication Number  
WO 02/096887 A1

(51) International Patent Classification<sup>7</sup>: C07D 239/47,  
A61K 31/505, C07D 405/12, 413/12, 401/12, A61P 35/00

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(21) International Application Number: PCT/GB02/02428

(22) International Filing Date: 24 May 2002 (24.05.2002)

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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
0113041.8 30 May 2001 (30.05.2001) GB

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, FR, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,  
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,  
VN, YU, ZA, ZM, ZW.

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BF, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CY, CZ,  
DE, DK, DM, DZ, EC, EE, ES, FI, FR, GB, GD, GE, GH,  
GM, GR, HR, HU, ID, IE, IL, IN, IS, IT, JP, KE, KG, KP,  
KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MC, MD, MK,  
MN, MW, MX, MZ, NL, NO, NZ, OM, PH, PL, PT, RO, RU,  
SD, SE, SG, SI, SK, SL, SZ, TJ, TM, TN, TR, TT, TZ, UA,  
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(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,  
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent  
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,  
NE, SN, TD, TG).

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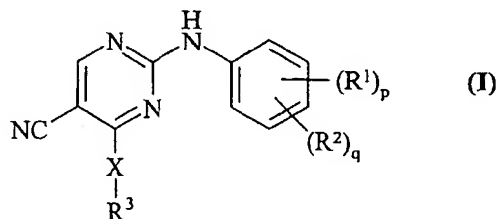
Published:  
— with international search report

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*For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: 2-ANILINO-PYRIMIDINE DERIVATIVES AS CYCLIN DEPENDENT KINASE INHIBITORS



(57) Abstract: Compounds of the formula (I): wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, p, q, and X are as defined within and a pharmaceutically acceptable salts and *in vivo* hydrolysable esters are described. Also described are processes for their preparation and their use as medicaments, particularly medicaments for producing a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal, such as man.

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## 2-ANILINO-PYRIMIDINE DERIVATIVES AS CYCLIN DEPENDENT KINASE INHIBITORS

The invention relates to pyrimidine derivatives, or pharmaceutically acceptable salts or *in vivo* hydrolysable esters thereof, which possess cell-cycle inhibitory activity and are accordingly useful for their anti-cell-proliferation (such as anti-cancer) activity and are therefore useful in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said pyrimidine derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments of use in the production of an anti-cell-proliferation effect in a warm-blooded animal such as man.

10 A family of intracellular proteins called cyclins play a central role in the cell cycle. The synthesis and degradation of cyclins is tightly controlled such that their level of expression fluctuates during the cell cycle. Cyclins bind to cyclin-dependent serine/threonine kinases (CDKs) and this association is essential for CDK (such as CDK1, CDK2, CDK4 and/or CDK6) activity within the cell. Although the precise details of how each of these factors  
15 combine to regulate CDK activity is poorly understood, the balance between the two dictates whether or not the cell will progress through the cell cycle.

The recent convergence of oncogene and tumour suppressor gene research has identified regulation of entry into the cell cycle as a key control point of mitogenesis in tumours. Moreover, CDKs appear to be downstream of a number of oncogene signalling  
20 pathways. Disregulation of CDK activity by upregulation of cyclins and/or deletion of endogenous inhibitors appears to be an important axis between mitogenic signalling pathways and proliferation of tumour cells.

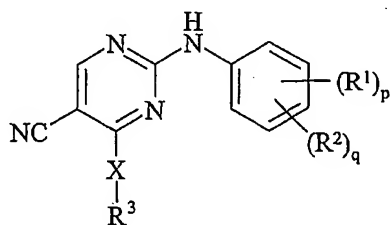
Accordingly it has been recognised that an inhibitor of cell cycle kinases, particularly inhibitors of CDK2, CDK4 and/or CDK6 (which operate at the S-phase, G1-S and G1-S phase  
25 respectively) should be of value as a selective inhibitor of cell proliferation, such as growth of mammalian cancer cells.

The present invention is based on the discovery that certain pyrimidine compounds surprisingly inhibit the effects of cell cycle kinases showing selectivity for CDK2, CDK4 and CDK6, and thus possess anti-cell-proliferation properties. Such properties are expected to be  
30 of value in the treatment of disease states associated with aberrant cell cycles and cell proliferation such as cancers (solid tumours and leukemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma,

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acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

Accordingly, the present invention provides a compound of formula (I):



(I)

wherein:

X is -O- or -S-;

R¹ is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto,

10 C₁-₆alkyl, C₂-₆alkenyl and C₂-₆alkynyl;

p is 0-4; wherein the values of R¹ may be the same or different;

R² is selected from sulphamoyl and a group R⁴-E-;

q is 0-2; wherein the values of R² maybe the same or different; and wherein p + q = 1-

5;

15 R³ is selected from C₁-₆alkyl, C₂-₆alkenyl, C₂-₆alkynyl, C₃-₈cycloalkyl and heterocyclyl; wherein R³ may be optionally substituted by one or more R⁵; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R⁶; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R⁷;

20 R⁴ is selected from C₁-₆alkyl, C₂-₆alkenyl, C₂-₆alkynyl, C₃-₈cycloalkyl, C₃-₈cycloalkylC₁-₆alkyl, phenyl, a heterocyclic group, phenylC₁-₆alkyl and (heterocyclic group)C₁-₆alkyl; wherein R⁴ may be optionally substituted on carbon by one or more R⁸; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R⁹;

25 E is selected from -C(O)-, -N(Rᵃ)C(O)-, -C(O)N(Rᵃ)-, -S(O)ᵣ-, -SO₂N(Rᵃ)- and -N(Rᵃ)SO₂-; wherein Rᵃ is hydrogen or C₁-₆alkyl optionally substituted by one or more R¹⁰ and r is 1-2;

- $R^5$  is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ alkanoyl,  $C_{1-6}$ alkanoyloxy,  $N$ -( $C_{1-6}$ alkyl)amino,  $N,N$ -( $C_{1-6}$ alkyl)<sub>2</sub>amino,  $C_{1-6}$ alkanoylamino,  $N$ -( $C_{1-6}$ alkyl)carbamoyl,  $N,N$ -( $C_{1-6}$ alkyl)<sub>2</sub>carbamoyl,  $C_{1-6}$ alkylS(O)<sub>a</sub>
- 5 wherein  $a$  is 0 to 2,  $C_{1-6}$ alkoxycarbonyl,  $N$ -( $C_{1-6}$ alkyl)sulphamoyl,  $N,N$ -( $C_{1-6}$ alkyl)<sub>2</sub>sulphamoyl,  $C_{3-8}$ cycloalkyl, phenyl and a heterocyclic group; wherein  $R^5$  may be optionally substituted on carbon by one or more  $R^{11}$ ; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from  $R^{12}$ ;
- $R^6$ ,  $R^7$ ,  $R^9$  and  $R^{12}$  are independently selected from  $C_{1-4}$ alkyl,  $C_{1-4}$ alkanoyl,
- 10  $C_{1-4}$ alkylsulphonyl,  $C_{1-4}$ alkoxycarbonyl, carbamoyl,  $N$ -( $C_{1-4}$ alkyl)carbamoyl,  $N,N$ -( $C_{1-4}$ alkyl)<sub>2</sub>carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; wherein  $R^6$ ,  $R^7$ ,  $R^9$  and  $R^{12}$  may be independently optionally substituted on carbon by one or more  $R^{13}$ ;
- $R^8$  and  $R^{10}$  are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl,
- 15  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ alkanoyl,  $C_{1-6}$ alkanoyloxy,  $N$ -( $C_{1-6}$ alkyl)amino,  $N,N$ -( $C_{1-6}$ alkyl)<sub>2</sub>amino,  $C_{1-6}$ alkanoylamino,  $N$ -( $C_{1-6}$ alkyl)carbamoyl,  $N,N$ -( $C_{1-6}$ alkyl)<sub>2</sub>carbamoyl,  $C_{1-6}$ alkylS(O)<sub>a</sub> wherein  $a$  is 0 to 2,  $C_{1-6}$ alkoxycarbonyl,  $N$ -( $C_{1-6}$ alkyl)sulphamoyl and  $N,N$ -( $C_{1-6}$ alkyl)<sub>2</sub>sulphamoyl; wherein  $R^8$  and  $R^{10}$  may be independently optionally substituted on carbon by one or more  $R^{14}$ ; and
- 20  $R^{11}$ ,  $R^{13}$  and  $R^{14}$  are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxyl, methylamino, ethylamino, dimethylamino, diethylamino,  $N$ -methyl- $N$ -ethylamino, acetylamino,  $N$ -methylcarbamoyl,  $N$ -ethylcarbamoyl,  $N,N$ -dimethylcarbamoyl,  $N,N$ -diethylcarbamoyl,  $N$ -methyl- $N$ -ethylcarbamoyl, methylthio,
- 25 ethylthio, methylsulphanyl, ethylsulphanyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl,  $N$ -methylsulphamoyl,  $N$ -ethylsulphamoyl,  $N,N$ -dimethylsulphamoyl,  $N,N$ -diethylsulphamoyl or  $N$ -methyl- $N$ -ethylsulphamoyl;
- or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

- In this specification the term "alkyl" includes both straight and branched chain alkyl
- 30 groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, " $C_{1-6}$ alkyl" includes  $C_{1-4}$ alkyl,  $C_{1-3}$ alkyl, propyl, isopropyl and *t*-butyl. However, references to individual alkyl groups such as 'propyl' are specific for

the straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. A similar convention applies to other radicals, for example "phenylC<sub>1-6</sub>alkyl" includes phenylC<sub>1-4</sub>alkyl, benzyl, 1-phenylethyl and 2-phenylethyl. The term "halo" refers to fluoro, chloro, bromo and iodo.

5       Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

A "heterocyclic group" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 4-12 atoms of which at least one atom is chosen from nitrogen,  
 10 sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH<sub>2</sub>- group can optionally be replaced by a -C(O)- and a ring sulphur atom may be optionally oxidised to form (the) S-oxide(s). Examples of the term "heterocyclic group" are morpholino, piperidyl, pyridyl, pyranyl, pyrrolyl, isothiazolyl, indolyl, quinolyl, thienyl, 1,3-benzodioxolyl, thiadiazolyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholino,  
 15 pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, tetrahydropyranyl, imidazolyl, pyrimidyl, pyrazinyl, pyridazinyl, isoxazolyl, *N*-methylpyrrolyl, 4-pyridone, 1-isoquinolone, 2-pyrrolidone, 4-thiazolidone, pyridine-*N*-oxide and quinoline-*N*-oxide. In one aspect of the invention a "heterocyclic group" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen,  
 20 sulphur or oxygen, it may, unless otherwise specified, be carbon or nitrogen linked, a -CH<sub>2</sub>- group can optionally be replaced by a -C(O)- and a ring sulphur atom may be optionally oxidised to form (the) S-oxide(s). In another aspect of the invention a "heterocyclic group" is morpholinyl, tetrahydrofuryl, piperidinyl, pyridyl, imidazolyl, piperazinyl, pyrrolidinyl, triazolyl, dioxanyl and dioxolanyl. In a further aspect of the invention, a "heterocyclic group"  
 25 is morpholinyl, piperidinyl and tetrahydrofuryl.

A "heterocyclyl" is a saturated mono or bicyclic ring containing 4-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH<sub>2</sub>- group can optionally be replaced by a -C(O)- and a ring sulphur atom may be optionally oxidised to form (the) S-oxide(s). Examples  
 30 of the term "heterocyclyl" are morpholinyl, piperidyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, homopiperazinyl, tetrahydropyranyl, 2-pyrrolidone and 4-thiazolidone. In one aspect of the invention a "heterocyclyl" is a saturated monocyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen,

sulphur or oxygen, it may, unless otherwise specified, be carbon or nitrogen linked, a -CH<sub>2</sub>- group can optionally be replaced by a -C(O)- and a ring sulphur atom may be optionally oxidised to form (the) S-oxide(s). In another aspect of the invention a "heterocyclyl" is tetrahydrofuryl.

- 5 An example of "C<sub>1-6</sub>alkanoyloxy" is acetoxy. Examples of "C<sub>1-6</sub>alkoxycarbonyl" include C<sub>1-4</sub>alkoxycarbonyl, methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C<sub>1-6</sub>alkoxy" include methoxy, ethoxy and propoxy. Examples of "C<sub>1-6</sub>alkanoylamino" include formamido, acetamido and propionylamino. Examples of "C<sub>1-6</sub>alkylS(O)<sub>a</sub> wherein a is 0 to 2" include C<sub>1-4</sub>alkylsulphonyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C<sub>1-6</sub>alkylS(O)<sub>r</sub>,  
10 wherein r is 1 to 2" include methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C<sub>1-6</sub>alkanoyl" include C<sub>1-4</sub>alkanoyl, propionyl and acetyl. Examples of "N-C<sub>1-6</sub>alkylamino" include methylamino and ethylamino. Examples of "N,N-(C<sub>1-6</sub>alkyl)<sub>2</sub>amino" include di-*N*-methylamino, di-(*N*-ethyl)amino and  
15 *N*-ethyl-*N*-methylamino. Examples of "C<sub>2-6</sub>alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C<sub>2-6</sub>alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "N-(C<sub>1-6</sub>alkyl)sulphamoyl" are *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "N-(C<sub>1-6</sub>alkyl)<sub>2</sub>sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "N-(C<sub>1-6</sub>alkyl)carbamoyl" are  
20 *N*-(C<sub>1-4</sub>alkyl)carbamoyl, methylaminocarbonyl and ethylaminocarbonyl. Examples of "N,N-(C<sub>1-6</sub>alkyl)<sub>2</sub>carbamoyl" are *N,N*-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl, dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "C<sub>3-8</sub>cycloalkyl" are cyclopropyl, cyclobutyl, cyclopropyl and cyclohexyl. Examples of "(heterocyclic group)C<sub>1-6</sub>alkyl" include pyridylmethyl, 3-morpholinopropyl and 2-pyrimid-2-ylethyl. Examples of  
25 "C<sub>3-8</sub>cycloalkylC<sub>1-6</sub>alkyl" are cyclopropylethyl, cyclobutylmethyl, 2-cyclopropylpropyl and cyclohexylethyl.

- A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example  
30 hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an

organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The compounds of the formula (I) may be administered in the form of an *in vivo* hydrolysable ester which is broken down in the human or animal body to give a compound of the formula (I).

An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C<sub>1-6</sub>alkoxymethyl esters for example methoxymethyl, C<sub>1-6</sub>alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C<sub>3-8</sub>cycloalkoxycarbonyloxyC<sub>1-6</sub>alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C<sub>1-6</sub>alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and  $\alpha$ -acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of  $\alpha$ -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazin-1-yl linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

Some compounds of the formula (I) may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess CDK inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess CDK inhibitory activity.

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess CDK inhibitory activity.

- 5 Further values of  $R^1$ ,  $R^2$ ,  $R^3$ ,  $p$  and  $q$  are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

X is -O-.

X is -S-.

- 10  $R^1$  is halo or  $C_{1-2}$ alkyl.

$R^1$  is fluoro, chloro or methyl.

$R^1$  is fluoro or chloro.

$p$  is 0-2; wherein the values of  $R^1$  may be the same or different.

$p$  is 0 or 1.

- 15  $p$  is 0.

$p$  is 1.

$p$  is 2; wherein the values of  $R^1$  may be the same or different.

$p$  is 1 and  $R^1$  is meta to the amino group in the aniline of formula (I).

$R^2$  is sulphamoyl or a group  $R^4$ -E-; wherein:

- 20  $R^4$  is selected from  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{3-8}$ cycloalkyl and (heterocyclic group) $C_{1-6}$ alkyl; wherein  $R^4$  may be optionally substituted on carbon by one or more  $R^8$ ;

E is selected from -S(O) $_r$ - and -N( $R^a$ )SO $_2$ -; wherein  $R^a$  is hydrogen or  $C_{1-6}$ alkyl and  $r$  is 2; and

- 25  $R^8$  is selected from halo,  $C_{1-6}$ alkoxy and  $N$ -( $C_{1-6}$ alkyl)amino.

$R^2$  is sulphamoyl or a group  $R^4$ -E-; wherein:

$R^4$  is selected from ethyl, propyl, butyl, allyl, cyclopropyl, tetrahydrofuran-2-ylmethyl and piperidinoethyl; wherein  $R^4$  may be optionally substituted on carbon by one or more  $R^8$ ;

E is selected from -S(O) $_2$ -, -NHSO $_2$ - and -N(Me)SO $_2$ -; and

- 30  $R^8$  is selected from fluoro, methoxy and isopropylamino.

$R^2$  is sulphamoyl,  $N,N$ -dimethylsulphamoyl,  $N$ -(cyclopropyl)sulphamoyl,  $N$ -(2-methoxyethyl)sulphamoyl,  $N$ -(3-methoxypropyl)sulphamoyl,  $N$ -(2,2,2-trifluoroethyl)sulphamoyl, ethylsulphonyl, 4-(isopropylamino)butylsulphonyl,  $N$ -



(allyl)sulphamoyl *N*-(tetrahydrofur-2-ylmethyl)sulphamoyl and *N*-(2-piperidinoethyl)sulphamoyl.

$R^2$  is sulphamoyl or a group  $R^4$ -E-; wherein:

$R^4$  is selected from  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{3-8}$ cycloalkyl,  $C_{3-8}$ cycloalkyl $C_{1-6}$ alkyl, and  
 5 (heterocyclic group) $C_{1-6}$ alkyl; wherein  $R^4$  may be optionally substituted on carbon by one or more  $R^8$ ;

E is selected from  $-S(O)_r-$  and  $-N(R^a)SO_2-$ ; wherein  $R^a$  is hydrogen or  $C_{1-6}$ alkyl and r is  
 2; and

$R^8$  is selected from halo,  $C_{1-6}$ alkoxy and *N*-( $C_{1-6}$ alkyl)amino.

10  $R^2$  is sulphamoyl or a group  $R^4$ -E-; wherein:

$R^4$  is selected from methyl, ethyl, propyl, butyl, allyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, tetrahydrofur-2-ylmethyl and piperidinoethyl; wherein  $R^4$  may be optionally substituted on carbon by one or more  $R^8$ ;

E is selected from  $-S(O)_2-$ ,  $-NHSO_2-$  and  $-N(Me)SO_2-$ ; and

15  $R^8$  is selected from fluoro, methoxy and isopropylamino.

$R^2$  is sulphamoyl, *N,N*-dimethylsulphamoyl, *N*-(cyclopropyl)sulphamoyl, *N*-(2-methoxyethyl)sulphamoyl, *N*-(3-methoxypropyl)sulphamoyl, *N*-(2,2,2-trifluoroethyl)sulphamoyl, ethylsulphonyl, 4-(isopropylamino)butylsulphonyl, *N*-(allyl)sulphamoyl *N*-(tetrahydrofur-2-ylmethyl)sulphamoyl, *N*-(2-piperidinoethyl)sulphamoyl,  
 20 *N*-(methyl)sulphamoyl, *N*-(methyl)-*N*-(2-methoxyethyl)sulphamoyl, *N*-(cyclobutyl)sulphamoyl and *N*-(cyclopropylmethyl)sulphamoyl.

E is  $-NHSO_2-$ ,  $-N(Me)SO_2-$  or  $-SO_2-$ .

E is  $-NHSO_2-$  or  $-SO_2-$ .

E is  $-NHSO_2-$ .

25 E is  $-SO_2-$ .

q is 0 or 1.

q is 0.

q is 1.

q is 2; wherein the values of  $R^2$  may be the same or different.

30 p + q = 1 or 2.

p + q = 1.

q is 1 and  $R^2$  is meta or para to the amino group in the aniline of formula (I).

q is 1 and  $R^2$  is para to the amino group in the aniline of formula (I).

R<sup>3</sup> is selected from C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkynyl and heterocyclyl; wherein R<sup>3</sup> may be optionally substituted by one or more R<sup>5</sup>; wherein:

R<sup>5</sup> is selected from C<sub>1-6</sub>alkoxy, C<sub>3-8</sub>cycloalkyl and a heterocyclic group; wherein R<sup>5</sup> may be optionally substituted on carbon by one or more R<sup>11</sup>; and

5 R<sup>11</sup> is methoxy.

R<sup>3</sup> is selected from methyl, ethyl, isopropyl, butyl, 2-propynyl, 2-butylnyl, 3-butylnyl, 3-butyln-2-yl and tetrahydrofuryl; wherein R<sup>3</sup> may be optionally substituted by one or more R<sup>5</sup>; wherein:

R<sup>5</sup> is selected from methoxy, ethoxy, cyclopropyl, morpholinyl and tetrahydrofuryl; 10 wherein R<sup>5</sup> may be optionally substituted on carbon by one or more R<sup>11</sup>; and

R<sup>11</sup> is methoxy.

R<sup>3</sup> is selected from methoxy, ethoxy, isopropoxy, butoxy, butylthio, 2-(2-methoxyethoxy)ethyl, 2-methoxyethoxy, tetrahydrofur-3-yloxy, tetrahydrofur-3-ylmethoxy, cyclopropylmethoxy, 2-propynyloxy, 2-butyntyloxy, 3-butyntyloxy, 3-butyln-2-yloxy and 2- 15 morpholinoethoxy.

R<sup>3</sup>-X- is selected from methoxy, ethoxy, isopropoxy, butoxy, butylthio, 2-(2-methoxyethoxy)ethoxy, 2-methoxyethoxy, tetrahydrofur-3-yloxy, tetrahydrofur-3-ylmethoxy, cyclopropylmethoxy, 2-propynyloxy, 2-butyntyloxy, 3-butyntyloxy, 3-butyln-2-yloxy and 2-morpholinoethoxy.

20 R<sup>3</sup> is selected from methyl, ethyl, isopropyl, butyl, 2-(2-methoxyethoxy)ethyl, 2-methoxyethyl, tetrahydrofur-3-yl, tetrahydrofur-3-ylmethyl, cyclopropylmethyl, 2-propynyl, 2-butylnyl, 3-butylnyl, 3-butyln-2-yl and 2-morpholinoethyl.

R<sup>3</sup> is selected from methyl, ethyl, isopropyl, butyl, but-2-yl, 2-propynyl, 2-butylnyl, 3-butylnyl, 3-butyln-2-yl and tetrahydrofuryl; wherein R<sup>3</sup> may be optionally substituted by one or 25 more R<sup>5</sup>; wherein:

R<sup>5</sup> is selected from methoxy, ethoxy, cyclopropyl, morpholinyl and tetrahydrofuryl; wherein R<sup>5</sup> may be optionally substituted on carbon by one or more R<sup>11</sup>; and

R<sup>11</sup> is methoxy.

R<sup>3</sup> is selected from methyl, ethyl, isopropyl, butyl, but-2-yl, 2-(2-methoxyethoxy)ethyl, 2-methoxyethyl, tetrahydrofur-3-yl, tetrahydrofur-3-ylmethyl, cyclopropylmethyl, 2- 30 propynyl, 2-butylnyl, 3-butylnyl, 3-butyln-2-yl and 2-morpholinoethyl.

R<sup>3</sup>-X- is selected from methoxy, ethoxy, isopropoxy, butoxy, but-2-yloxy, butylthio, 2-(2-methoxyethoxy)ethoxy, 2-methoxyethoxy, tetrahydrofur-3-yloxy, tetrahydrofur-3-

ylmethoxy, cyclopropylmethoxy, 2-propynyloxy, 2-butynyloxy, 3-butynyloxy, 3-butyn-2-yloxy and 2-morpholinoethoxy.

Therefore in one aspect of the invention, there is provided a compound of formula (I) as depicted above wherein:

- 5 X is -O- or -S-;  
 p is 0;  
 R<sup>2</sup> is sulphonyl or a group R<sup>4</sup>-E-; wherein:  
 R<sup>4</sup> is selected from C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>3-8</sub>cycloalkyl and  
 (heterocyclic group)C<sub>1-6</sub>alkyl; wherein R<sup>4</sup> may be optionally substituted on carbon by one or  
 10 more R<sup>8</sup>;  
 E is selected from -S(O)<sub>r</sub>- and -N(R<sup>a</sup>)SO<sub>2</sub>-; wherein R<sup>a</sup> is hydrogen or C<sub>1-6</sub>alkyl and r is  
 2;  
 R<sup>8</sup> is selected from halo, C<sub>1-6</sub>alkoxy and N-(C<sub>1-6</sub>alkyl)amino;  
 q is 1;  
 15 R<sup>3</sup> is selected from C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkynyl and heterocyclyl; wherein R<sup>3</sup> may be  
 optionally substituted by one or more R<sup>5</sup>; wherein:  
 R<sup>5</sup> is selected from C<sub>1-6</sub>alkoxy, C<sub>3-8</sub>cycloalkyl and a heterocyclic group; wherein R<sup>5</sup>  
 may be optionally substituted on carbon by one or more R<sup>11</sup>; and  
 R<sup>11</sup> is methoxy;  
 20 or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Therefore in a further aspect of the invention, there is provided a compound of formula (II) as depicted above wherein:

- X is -O- or -S-;  
 p is 0;  
 25 R<sup>2</sup> is sulphonyl or a group R<sup>4</sup>-E-; wherein:  
 R<sup>4</sup> is selected from ethyl, propyl, butyl, allyl, cyclopropyl, tetrahydrofur-2-ylmethyl  
 and piperidinoethyl; wherein R<sup>4</sup> may be optionally substituted on carbon by one or more R<sup>8</sup>;  
 E is selected from -S(O)<sub>2</sub>-, -NHSO<sub>2</sub>- and -N(Me)SO<sub>2</sub>-;  
 R<sup>8</sup> is selected from fluoro, methoxy and isopropylamino;  
 30 q is 1;  
 R<sup>3</sup> is selected from methyl, ethyl, isopropyl, butyl, 2-propynyl, 2-butynyl, 3-butynyl, 3-butyn-2-yl and tetrahydrofuryl; wherein R<sup>3</sup> may be optionally substituted by one or more R<sup>5</sup>;  
 wherein:

$R^5$  is selected from methoxy, ethoxy, cyclopropyl, morpholinyl and tetrahydrofuryl; wherein  $R^5$  may be optionally substituted on carbon by one or more  $R^{11}$ ; and

$R^{11}$  is methoxy;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

5 Therefore in another further aspect of the invention, there is provided a compound of formula (I) (as depicted above); wherein:

X is -O- or -S-;

p is 0;

$R^2$  is sulphamoyl, *N,N*-dimethylsulphamoyl, *N*-(cyclopropyl)sulphamoyl, *N*-(2-methoxyethyl)sulphamoyl, *N*-(3-methoxypropyl)sulphamoyl, *N*-(2,2,2-trifluoroethyl)sulphamoyl, ethylsulphonyl, 4-(isopropylamino)butylsulphonyl, *N*-(allyl)sulphamoyl, *N*-(tetrahydrofur-2-ylmethyl)sulphamoyl and *N*-(2-piperidinoethyl)sulphamoyl;

q is 1; and

15  $R^3$  is selected from methoxy, ethoxy, isopropoxy, butoxy, butylthio, 2-(2-methoxyethoxy)ethyl, 2-methoxyethoxy, tetrahydrofur-3-yloxy, tetrahydrofur-3-ylmethoxy, cyclopropylmethoxy, 2-propynyloxy, 2-butyloxy, 3-butyloxy, 3-buten-2-yloxy and 2-morpholinoethoxy;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

20 Therefore in one aspect of the invention, there is provided a compound of formula (I) as depicted above wherein:

X is -O- or -S-;

p is 0;

$R^2$  is sulphamoyl or a group  $R^4$ -E-; wherein:

25  $R^4$  is selected from  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{3-8}$ cycloalkyl,  $C_{3-8}$ cycloalkyl $C_{1-6}$ alkyl, and (heterocyclic group) $C_{1-6}$ alkyl; wherein  $R^4$  may be optionally substituted on carbon by one or more  $R^8$ ;

E is selected from -S(O)<sub>r</sub>- and -N( $R^a$ )SO<sub>2</sub>-; wherein  $R^a$  is hydrogen or  $C_{1-6}$ alkyl and r is 2;

30  $R^8$  is selected from halo,  $C_{1-6}$ alkoxy and *N*-( $C_{1-6}$ alkyl)amino;

q is 1;

$R^3$  is selected from  $C_{1-6}$ alkyl,  $C_{2-6}$ alkynyl and heterocyclyl; wherein  $R^3$  may be optionally substituted by one or more  $R^5$ ; wherein:

$R^5$  is selected from  $C_{1-6}$ alkoxy,  $C_{3-8}$ cycloalkyl and a heterocyclic group; wherein  $R^5$  may be optionally substituted on carbon by one or more  $R^{11}$ ; and

$R^{11}$  is methoxy;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

5 Therefore in a further aspect of the invention, there is provided a compound of formula (I) as depicted above wherein:

X is -O- or -S-;

p is 0;

$R^2$  is sulphamoyl or a group  $R^4$ -E-; wherein:

10  $R^4$  is selected from methyl, ethyl, propyl, butyl, allyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, tetrahydrofur-2-ylmethyl and piperidinoethyl; wherein  $R^4$  may be optionally substituted on carbon by one or more  $R^8$ ;

E is selected from -S(O)<sub>2</sub>-, -NHSO<sub>2</sub>- and -N(Me)SO<sub>2</sub>-;

$R^8$  is selected from fluoro, methoxy and isopropylamino;

15 q is 1;

$R^3$  is selected from methyl, ethyl, isopropyl, butyl, but-2-yl, 2-propynyl, 2-butylnyl, 3-butylnyl, 3-butyln-2-yl and tetrahydrofuryl; wherein  $R^3$  may be optionally substituted by one or more  $R^5$ ; wherein:

$R^5$  is selected from methoxy, ethoxy, cyclopropyl, morpholinyl and tetrahydrofuryl;

20 wherein  $R^5$  may be optionally substituted on carbon by one or more  $R^{11}$ ; and

$R^{11}$  is methoxy;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Therefore in another further aspect of the invention, there is provided a compound of formula (I) (as depicted above); wherein:

25 X is -O- or -S-;

p is 0;

$R^2$  is sulphamoyl, *N,N*-dimethylsulphamoyl, *N*-(cyclopropyl)sulphamoyl, *N*-(2-methoxyethyl)sulphamoyl, *N*-(3-methoxypropyl)sulphamoyl, *N*-(2,2,2-trifluoroethyl)sulphamoyl, ethylsulphonyl, 4-(isopropylamino)butylsulphonyl, *N*-(allyl)sulphamoyl, *N*-(tetrahydrofur-2-ylmethyl)sulphamoyl, *N*-(2-piperidinoethyl)sulphamoyl, *N*-(methyl)sulphamoyl, *N*-(methyl)-*N*-(2-methoxyethyl)sulphamoyl, *N*-(cyclobutyl)sulphamoyl and *N*-(cyclopropylmethyl)sulphamoyl;

30 q is 1; and

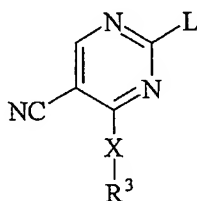
$R^3$  is selected from methyl, ethyl, isopropyl, butyl, but-2-yl, 2-(2-methoxyethoxy)ethyl, 2-methoxyethyl, tetrahydrofur-3-yl, tetrahydrofur-3-ylmethyl, cyclopropylmethyl, 2-propynyl, 2-butyryl, 3-butyryl, 3-butyryl-2-yl and 2-morpholinoethyl; or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

5 In another aspect of the invention, preferred compounds of the invention are any one of the Examples or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Preferred aspects of the invention are those which relate to the compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention provides a process for preparing a compound  
10 of formula (I) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof which process (wherein  $R^1$ ,  $R^2$ ,  $R^3$ , p and q are, unless otherwise specified, as defined in formula (I)) comprises of:

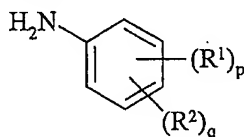
a) reaction of a pyrimidine of formula (II):



(II)

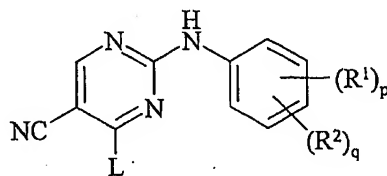
15

wherein L is a displaceable group; with an aniline of formula (III):



(III)

b) reacting a pyrimidine of formula (IV):



(IV)

20

wherein L is a displaceable group; with a compound of formula (V):

- 14 -

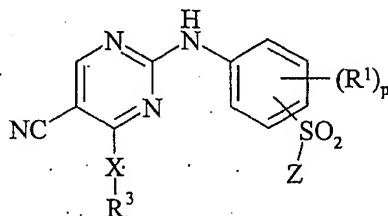


(V)

or

c) for compounds of formula (I) where  $R^2$  is sulhamoyl or a group  $R^4-E$  and E is  $-NHSO_2-$ ;

5 reacting a pyrimidine of formula (VI):



(VI)

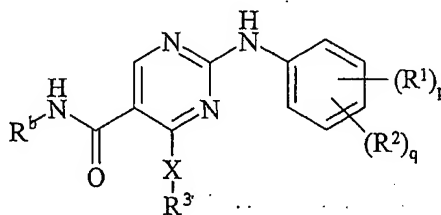
wherein Z is a displaceable group; with an amine of formula (VII):



(VII)

10

d) by converting a compound of formula (VIII):



(VIII)

wherein  $R^b$  is hydrogen or *t*-butyl; into a compound of formula (I);

15 and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

L is a displaceable group, suitable values for L are for example, a halogeno, an

20 optionally substituted phenoxy or sulphonyloxy group, for example a chloro, bromo, phenoxy, 4-chlorophenoxy, methanesulphonyloxy or toluene-4-sulphonyloxy group.

Z is a displaceable group, suitable values for Z are for example, a halogeno group, for example a fluoro, chloro or bromo group. Preferably Z is fluoro.

Preferably T is S.

25

Specific reaction conditions for the above reactions are as follows.

- a) Pyrimidines of formula (II) and anilines of formula (III) may be reacted together:
- i) in the presence of a suitable solvent for example a ketone such as acetone or an alcohol such as ethanol or butanol or an aromatic hydrocarbon such as toluene or *N*-methyl pyrrolidine, optionally in the presence of a suitable acid for example an inorganic acid such as hydrochloric acid or sulphuric acid, or an organic acid such as acetic acid or formic acid (or a suitable Lewis acid) and at a temperature in the range of 0°C to reflux, preferably reflux; or
  - ii) under standard Buchwald conditions (for example see *J. Am. Chem. Soc.*, 118, 7215; *J. Am. Chem. Soc.*, 119, 8451; *J. Org. Chem.*, 62, 1568 and 6066) for example in the presence of palladium acetate, in a suitable solvent for example an aromatic solvent such as toluene, benzene or xylene, with a suitable base for example an inorganic base such as caesium carbonate or an organic base such as potassium-*t*-butoxide, in the presence of a suitable ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and at a temperature in the range of 25 to 80°C.

Pyrimidines of the formula (II) and anilines of formula (III) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

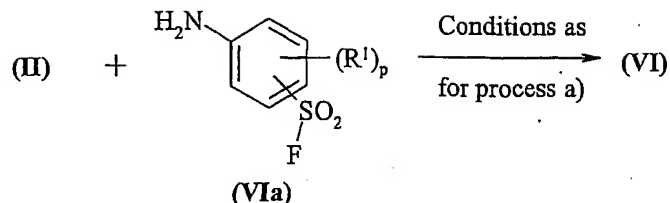
- b) Pyrimidines of formula (IV) and compounds of formula (V) may be reacted together:
- i) under the conditions described under process a) i); or
  - ii) in the presence of a suitable solvent for example a ketone such as acetone or an alcohol such as ethanol or butanol or an aromatic hydrocarbon such as toluene or *N*-methyl pyrrolidine, in the presence of a suitable base for example an alkoxide such as sodium ethoxide or potassium *t*-butoxide, and at a temperature in the range of 0°C to reflux, preferably reflux.

Pyrimidines of the formula (IV) and compounds of formula (V) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

- c) Compounds of formula (VI) and compounds of formula (VII) may be reacted together in the presence of a base for example an inorganic base such as caesium carbonate in the presence of an inert solvent such as toluene or tetrahydrofuran, or in the presence of an organic base such as excess (VII) and at a temperature in the range of 25 to 80°C.

Compounds of formula (VI) wherein Z is fluoro may be prepared according to the following scheme:

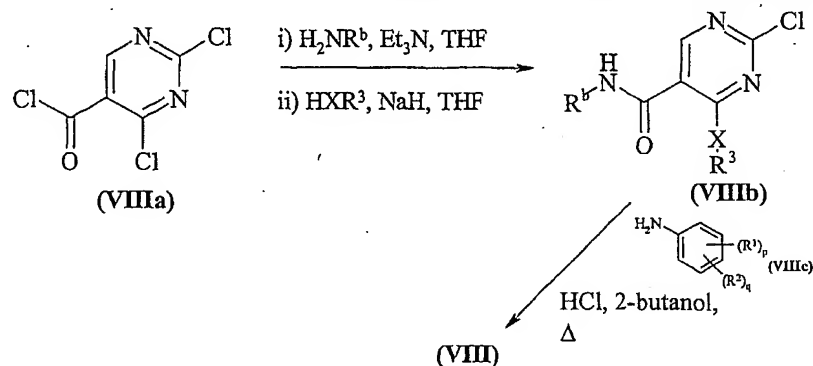




Compounds of formula (VIa) and (VII) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

- d) Compounds of formula (VIII) may be converted into compounds of formula (I) under standard conditions, for example in the presence of trifluoroacetic anhydride (where  $R^b$  is hydrogen) or thionyl chloride at a temperature in the range of 25 to 100°C.

Compounds of formula (VIII) may be prepared according to the following scheme:



- Compounds of formula (VIIIa) and (VIIIc) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts

conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

5 It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, *Protective Groups in Organic Synthesis*, John Wiley  
10 and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group,  
15 for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such  
20 as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a  
25 primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting  
30 groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide.

Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis  
5 with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using  
10 conventional techniques well known in the chemical art.

As stated hereinbefore the compounds defined in the present invention possesses anti-cell-proliferation activity such as anti-cancer activity which is believed to arise from the CDK inhibitory activity of the compound. These properties may be assessed, for example, using the assay as set out in WO 01/14375, page 27-30, which is incorporated herein by  
15 reference. Although the pharmacological properties of the compounds of the formula (I) vary with structural change, in general activity possessed by compounds of the formula (I) in this assay may be demonstrated at IC<sub>50</sub> concentrations or doses in the range 250µM to 1nM.

The *in vivo* activity of the compounds of formula (I) may be measured in the SRB assay as set out in WO 01/14375, page 30-31, which is incorporated herein by reference.  
20 Typical IC<sub>50</sub> values for compounds of the invention when tested in the SRB assay are in the range 1mM to 1nM.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a pyrimidine derivative of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore  
25 in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.  
30 In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compound of formula (I) will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before, for use in a method of treatment of the human or animal body by therapy.

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, are effective cell cycle inhibitors (anti-cell proliferation agents), which property is believed to arise from their CDK inhibitory properties. Accordingly the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by CDK enzymes, i.e. the compounds may be used to produce a CDK inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of the present invention provide a method for treating the proliferation of malignant cells characterised by inhibition of CDK enzymes, i.e. the compounds may be used to produce an anti-proliferative effect mediated alone or in part by the inhibition of CDKs. Such a compound of the invention is expected to possess a wide range of anti-cancer properties as CDKs have been implicated in many common human cancers such as leukaemia and breast, lung, colon, rectal, stomach, prostate, bladder, pancreas and ovarian cancer. Thus it is expected that a compound of the invention will possess anti-cancer activity against these cancers. It is in addition expected that a compound of the present invention will possess activity against a range of leukaemias, lymphoid malignancies and solid tumours such as carcinomas and sarcomas in tissues such as the liver, kidney, prostate and pancreas. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such compounds of the invention, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, are expected to inhibit the growth of those primary and recurrent solid tumours which are

associated with CDKs, especially those tumours which are significantly dependent on CDKs for their growth and spread, including for example, certain tumours of the colon, breast, prostate, lung, vulva and skin.

It is further expected that a compound of the present invention will possess activity  
5 against other cell-proliferation diseases in a wide range of other disease states including leukaemias, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

10 Thus according to this aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before, for use as a medicament; and the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before, in the manufacture of a medicament for use in the production of a cell cycle inhibitory  
15 (anti-cell-proliferation) effect in a warm-blooded animal such as man. Particularly, an inhibitory effect is produced by preventing entry into or progression through the S phase by inhibition of CDK2, CDK4 and/or CDK6, especially CDK2.

According to a further feature of the invention, there is provided a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as  
20 defined herein before, in the manufacture of a medicament for use in the treatment of cancers (solid tumours and leukaemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, particularly  
25 in the treatment of cancers.

According to a further feature of this aspect of the invention there is provided a method for producing a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in*  
30 *vivo* hydrolysable ester thereof, as defined herein before. Particularly, an inhibitory effect is produced by preventing entry into or progression through the S phase by inhibition of CDK2, CDK4 and/or CDK6, especially CDK2.

According to an additional feature of this aspect of the invention there is provided a method of treating cancers (solid tumours and leukaemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before.

10        Particularly there is provided a method of treating cancer in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before.

15        In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before, in association with a pharmaceutically-acceptable diluent or carrier for use in the production of a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal such as man.

20        In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before, in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of cancers (solid tumours and leukaemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, in a warm-blooded animal such as man.

25        In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before, in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of cancer in a warm-blooded animal such as man.

Preventing cells from entering DNA synthesis by inhibition of essential S-phase initiating activities such as CDK2 initiation may also be useful in protecting normal cells of the body from toxicity of cycle-specific pharmaceutical agents. Inhibition of CDK2 or 4 will prevent progression into the cell cycle in normal cells which could limit the toxicity of cycle-specific pharmaceutical agents which act in S-phase, G2 or mitosis. Such protection may result in the prevention of hair loss normally associated with these agents.

Therefore in a further aspect of the invention there is provided a compound of formula (I) as defined above or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for use as a cell protective agent.

10 Therefore in a further aspect of the invention there is provided a compound of formula (I) as defined above or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for use in preventing hair loss arising from the treatment of malignant conditions with pharmaceutical agents.

Examples of pharmaceutical agents for treating malignant conditions that are known to cause hair loss include alkylating agents such as ifosfamide and cyclophosphamide; antimetabolites such as methotrexate, 5-fluorouracil, gemcitabine and cytarabine; vinca alkaloids and analogues such as vincristine, vinblastine, vindesine, vinorelbine; taxanes such as paclitaxel and docetaxel; topoisomerase I inhibitors such as irinotecan and topotecan; cytotoxic antibiotics such as doxorubicin, daunorubicin, mitoxantrone, actinomycin-D and mitomycin; and others such as etoposide and tretinoin.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, may be administered in association with one or more of the above pharmaceutical agents. In this instance the compound of formula (I) may be administered by systemic or non systemic means. Particularly the compound of formula (I) may be administered by non-systemic means, for example topical administration.

Therefore in an additional feature of the invention, there is provided a method of preventing hair loss during treatment for one or more malignant conditions with pharmaceutical agents, in a warm-blooded animal, such as man, which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

In an additional feature of the invention, there is provided a method of preventing hair loss during treatment for one or more malignant conditions with pharmaceutical agents, in a

warm-blooded animal, such as man, which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof in simultaneous, sequential or separate administration with an effective amount of said pharmaceutical agent.

5           According to a further aspect of the invention there is provided a pharmaceutical composition for use in preventing hair loss arising from the treatment of malignant conditions with pharmaceutical agents which comprises a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, and said pharmaceutical agent, in association with a pharmaceutically acceptable diluent or carrier.

10           According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, and a pharmaceutical agent for treating malignant conditions that is known to cause hair loss.

            According to a further aspect of the present invention there is provided a kit  
15 comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, in a first unit dosage form;
- b) a pharmaceutical agent for treating malignant conditions that is known to cause hair loss; in a second unit dosage form; and
- 20 c) container means for containing said first and second dosage forms.

            According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, in the manufacture of a medicament for the prevention of hair loss during treatment of malignant conditions with pharmaceutical agents.

25           According to a further aspect of the present invention there is provided a combination treatment for the prevention of hair loss comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of  
30 a pharmaceutical agent for treatment of malignant conditions to a warm-blooded animal, such as man.

            As stated above the size of the dose required for the therapeutic or prophylactic



treatment of a particular cell-proliferation disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-100 mg/kg; preferably 1-50 mg/kg is envisaged.

The CDK inhibitory activity defined hereinbefore may be applied as a sole therapy or  
5 may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint  
10 treatment in addition to the cell cycle inhibitory treatment defined hereinbefore may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

- (i) other cell cycle inhibitory agents that work by the same or different mechanisms from those defined hereinbefore;
- 15 (ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, idoxifene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luproline), inhibitors of testosterone  
20  $5\alpha$ -dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and  
25 serine/threonine kinase inhibitors); and
- (iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin  
30 and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); antimitotic

agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere);  
topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide,  
amsacrine, topotecan). According to this aspect of the invention there is provided a  
pharmaceutical product comprising a compound of the formula (I) as defined hereinbefore  
5 and an additional anti-tumour substance as defined hereinbefore for the conjoint treatment of  
cancer.

In addition to their use in therapeutic medicine, the compounds of formula (I) and their  
pharmaceutically acceptable salts are also useful as pharmacological tools in the development  
and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of  
10 inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats  
and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament  
manufacture features, the alternative and preferred embodiments of the compounds of the  
invention described herein also apply.

#### 15 Examples

The invention will now be illustrated by the following non limiting examples in which,  
unless stated otherwise:

- (i) temperatures are given in degrees Celsius (°C); operations were carried out at room or  
ambient temperature, that is, at a temperature in the range of 18-25°C;
- 20 (ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent  
was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals;  
4.5-30mmHg) with a bath temperature of up to 60°C;
- (iii) chromatography means flash chromatography on silica gel; thin layer chromatography  
(TLC) was carried out on silica gel plates;
- 25 (iv) in general, the course of reactions was followed by TLC and reaction times are given for  
illustration only;
- (v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or  
mass spectral data;
- (vi) yields are given for illustration only and are not necessarily those which can be obtained  
30 by diligent process development; preparations were repeated if more material was required;
- (vii) when given, NMR data is in the form of delta values for major diagnostic protons, given  
in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard,

determined at 300 MHz using perdeuterio dimethyl sulphoxide (DMSO-d<sub>6</sub>) as solvent unless otherwise indicated;

(viii) chemical symbols have their usual meanings; SI units and symbols are used;

(ix) solvent ratios are given in volume:volume (v/v) terms; and

- 5 (x) mass spectra were run with an electron energy of 70 electron volts in the chemical ionization (CI) mode using a direct exposure probe; where indicated ionization was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported; and unless otherwise stated, the mass ion quoted is (MH)<sup>+</sup>;

- 10 (xi) unless stated otherwise compounds containing an asymmetrically substituted carbon and/or sulphur atom have not been resolved;

(xii) where a synthesis is described as being analogous to that described in a previous example the amounts used are the millimolar ratio equivalents to those used in the previous example;

(xvi) the following abbreviations have been used:

- |    |     |                        |
|----|-----|------------------------|
| 15 | THF | tetrahydrofuran;       |
|    | SM  | starting material; and |
|    | DCM | dichloromethane.       |

### Example 1

- 20 2-{4-[N-(2-Methoxyethyl)sulphamoyl]anilino}-4-(2-propyn-1-yloxy)-5-cyanopyrimidine

A solution of 2-chloro-4-(2-propyn-1-yloxy)-5-cyanopyrimidine (Method 17; 219mg, 1.13mmol) and 4-[N-(2-methoxyethyl)sulphamoyl]aniline (Method 38; 130mg, 0.56mmol) in 2-butanol (8ml) was stirred at 50°C for 18 hours. Solvent was removed under reduced pressure and the product recrystallized from methanol to give the title compound (145mg,

- 25 67%). NMR: 2.90 (q, 2H), 3.15 (s, 3H), 3.25 (m, 2H), 3.70 (s, 1H), 5.20 (s, 2H), 7.55 (t, 1H), 7.75 (d, 2H), 7.90 (d, 2H), 8.80 (s, 1H); m/z 387.

### Examples 2-30

The following compounds were prepared using the procedure of Example 1 using the

- 30 appropriate pyrimidine and aniline starting materials.

Ex	Compound Name	NMR	m/z	SM	Aniline
2	2-(4-Ethylsulphonyl-anilino)-4-(2-tetrahydrofur-3-yloxy)-5-cyanopyrimidine	1.10 (t, 3H), 2.10 (m, 1H), 2.35 (m, 1H), 3.20 (m, 2H), 3.70-4.00 (m, 4H), 5.70 (br s, 1H), 7.80 (d, 2H), 7.95 (d, 2H), 7.75 (s, 1H)	374	Meth 18	Ref 1
3	2-{4-[N-(2,2,2-Trifluoroethyl)sulphamoyl]anilino}-4-(2-tetrahydrofur-3-yloxy)-5-cyanopyrimidine	2.10 (m, 1H), 2.30 (m, 1H), 3.65 (m, 2H), 3.70-4.00 (m, 4H), 5.70 (br s, 1H), 7.80 (d, 2H), 7.90 (d, 2H), 8.45 (t, 1H), 8.75 (s, 1H)	443	Meth 18	Meth 44
4	2-{4-[N-(3-Methoxypropyl)sulphamoyl]anilino}-4-(2-tetrahydrofur-3-yloxy)-5-cyanopyrimidine	1.55 (m, 2H), 2.10 (m, 1H), 2.30 (m, 1H), 2.75 (q, 2H), 3.10 (s, 3H), 3.25 (m, 2H), 3.70-3.95 (m, 4H), 5.70 (br s, 1H), 7.40 (t, 1H), 7.75 (d, 2H), 7.90 (d, 2H), 8.75 (s, 1H)	433	Meth 18	Meth 40
5	2-{4-[N-(2-Methoxyethyl)sulphamoyl]anilino}-4-(2-tetrahydrofur-3-yloxy)-5-cyanopyrimidine	2.10 (m, 1H), 2.35 (m, 1H), 2.90 (m, 2H), 3.20 (s, 3H), 3.30 (t, 2H), 3.75-4.00 (m, 4H), 5.70 (s, 1H), 7.55 (t, 1H), 7.80 (d, 2H), 7.90 (d, 2H), 8.75 (s, 1H), 10.70 (br s, 1H)	419	Meth 18	Meth 38
6	2-{4-[N-(3-Methoxypropyl)sulphamoyl]anilino}-4-(3-butyn-2-yloxy)-5-cyanopyrimidine	1.60 (m, 2H), 1.65 (d, 3H), 2.80 (m, 2H), 3.20 (s, 3H), 3.30 (t, 2H), 3.70 (s, 1H), 5.85 (m, 1H), 7.45 (t, 1H), 7.80 (d, 2H), 8.00 (d, 2H), 8.80 (s, 1H), 10.80 (br s, 1H)	415	Meth 23	Meth 40

7	2-{4-(4-Isopropylamino-butylsulphonyl)anilino}-4-(2-propyn-1-yloxy)-5-cyanopyrimidine	1.30 (d, 6H), 1.70 (br s, 4H), 2.90 (br s, 2H), 3.25 (m, 1H), 3.40 (m, 2H), 3.80 (s, 1H), 5.20 (s, 1H), 7.90 (d, 2H), 8.10 (d, 2H), 8.50 (brs, 1H), 8.85 (s, 1H), 10.90 (s, 1H)	427	Meth 17	Meth 49
8	2-{4-[N-(3-Methoxypropyl)sulphamoyl]anilino}-4-(2-propyn-1-yloxy)-5-cyanopyrimidine	1.60 (m, 2H), 2.75 (m, 2H), 3.10 (s, 3H), 3.25 (t, 2H), 3.70 (s, 1H), 5.15 (s, 2H), 7.40 (t, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.80 (s, 1H)	401	Meth 17	Meth 40
9	2-(4-Ethylsulphonyl-anilino)-4-(2-propyn-1-yloxy)-5-cyanopyrimidine	1.10 (t, 3H), 3.25 (q, 2H), 3.70 (s, 1H), 5.20 (s, 2H), 7.80 (d, 2H), 8.00 (d, 2H), 8.80 (s, 1H)	342	Meth 17	Ref 1
10	2-{4-[N-(2,2,2-Trifluoroethyl)sulphamoyl]anilino}-4-(2-propyn-1-yloxy)-5-cyanopyrimidine	3.65 (m, 2H), 3.70 (s, 1H), 5.20 (s, 2H), 7.80 (d, 2H), 7.95 (d, 2H), 8.45 (t, 1H), 8.80 (s, 1H)	411	Meth 17	Meth 44
11	2-[4-(N-Allyl sulphamoyl)anilino]-4-(2-propyn-1-yloxy)-5-cyanopyrimidine	3.40 (m, 2H), 3.70 (s, 1H), 5.00 (d, 1H), 5.10 (d, 1H), 5.20 (s, 2H), 5.65 (m, 1H), 7.65 (t, 1H), 7.75 (d, 2H), 7.90 (d, 2H), 8.80 (s, 1H)	369	Meth 17	Meth 42
12	2-{4-[N-(3-Methoxypropyl)sulphamoyl]anilino}-4-(2-butyn-1-yloxy)-5-cyanopyrimidine	1.55 (m, 2H), 1.85 (s, 3H), 2.75 (q, 2H), 3.10 (s, 3H), 3.25 (m, 2H), 5.15 (m, 2H), 7.40 (t, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.80 (s, 1H)	415	Meth 20	Meth 40

13	2-{4-[N-(3-Methoxypropyl)sulphamoyl]anilino}-4-(tetrahydrofur-3-ylmethoxy)-5-cyanopyrimidine	1.55 (m, 2H), 1.70 (m, 1H), 2.00 (m, 1H), 2.75 (m, 2H), 3.10 (s, 3H), 3.25 (m, 2H), 3.50 (m, 1H), 3.65 (m, 1H), 3.75 (m, 3H), 4.40 (m, 2H), 7.40 (t, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.70 (s, 1H)	447	Meth 19	Meth 40
14	2-{4-[N-(3-Methoxypropyl)sulphamoyl]anilino}-4-(3-butyn-1-yloxy)-5-cyanopyrimidine	1.55 (m, 2H), 2.70 (m, 4H), 2.90 (s, 1H), 3.10 (s, 3H), 3.25 (m, 2H), 4.55 (t, 2H), 7.40 (t, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.75 (s, 1H)	415	Meth 21	Meth 40
15	2-{4-[N-(3-Methoxypropyl)sulphamoyl]anilino}-4-(2-morpholinoethoxy)-5-cyanopyrimidine	1.60 (m, 2H), 2.45 (m, 4H), 2.70 (m, 4H), 3.15 (s, 3H), 3.25 (m, 2H), 3.50 (m, 4H), 4.60 (m, 2H), 7.45 (t, 1H), 7.75 (d, 2H), 7.90 (d, 2H), 8.75 (s, 1H), 10.75 (br s, 1H)	476	Meth 24	Meth 40
16	2-{4-[N-(3-Methoxypropyl)sulphamoyl]anilino}-4-[2-(2-methoxyethoxy)ethoxy]-5-cyanopyrimidine	1.60 (m, 2H), 2.75 (q, 2H), 3.10 (s, 3H), 3.20 (m, 5H), 3.45 (m, 2H), 3.60 (m, 2H), 3.80 (m, 2H), 4.60 (m, 2H), 7.40 (t, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.75 (s, 1H)	465	Meth 30	Meth 40
17	2-{4-[N-(3-Methoxypropyl)sulphamoyl]anilino}-4-(2-methoxyethoxy)-5-cyanopyrimidine	1.60 (m, 2H), 2.75 (q, 2H), 3.10 (s, 3H), 3.25 (t, 2H), 3.30 (s, 3H), 3.70 (m, 2H), 4.60 (m, 2H), 7.40 (t, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.75 (s, 1H)	421	Meth 22	Meth 40

18	2-{4-[N-(3-Methoxypropyl)sulphamoyl]anilino}-4-(cyclopropylmethoxy)-5-cyanopyrimidine	0.40 (m, 2H), 0.60 (m, 2H), 1.30 (m, 1H), 1.60 (m, 2H), 2.75 (m, 2H), 3.10 (s, 3H), 3.25 (t, 2H), 4.30 (d, 2H), 7.40 (t, 1H), 7.75 (d, 2H), 7.90 (d, 2H), 8.75 (s, 1H), 10.65 (br s, 1H)	417	Meth 25	Meth 40
19	2-{4-[N-(3-Methoxypropyl)sulphamoyl]anilino}-4-ethoxy-5-cyanopyrimidine	1.35 (t, 3H), 1.55 (m, 2H), 2.75 (m, 2H), 3.10 (s, 3H), 3.25 (m, 2H), 4.50 (m, 2H), 7.40 (t, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.70 (s, 1H)	391	Meth 31	Meth 40
20	2-{4-[N-(2,2,2-Trifluoroethyl)sulphamoyl]anilino}-4-isopropoxy-5-cyanopyrimidine	1.40 (d, 6H), 3.65 (m, 2H), 5.40 (m, 1H), 7.80 (d, 2H), 7.90 (d, 2H), 8.45 (t, 1H), 8.70 (s, 1H)	415	Meth 26	Meth 44
21	2-{4-[N-(3-Methoxypropyl)sulphamoyl]anilino}-4-isopropoxy-5-cyanopyrimidine	1.40 (d, 6H), 1.55 (m, 2H), 2.75 (q, 2H), 3.10 (s, 3H), 3.25 (m, 2H), 5.25 (m, 1H), 7.40 (t, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.70 (s, 1H)	405	Meth 26	Meth 40
22	2-{4-[N-(2-Methoxyethyl)sulphamoyl]anilino}-4-isopropoxy-5-cyanopyrimidine	1.40 (d, 6H), 2.85 (q, 2H), 3.15 (s, 3H), 3.25 (t, 2H), 5.45 (m, 1H), 7.55 (t, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.70 (s, 1H)	391	Meth 26	Meth 38
23	2-{4-[N-(3-Methoxypropyl)sulphamoyl]anilino}-4-methoxy-5-cyanopyrimidine	1.60 (m, 2H), 2.80 (q, 2H), 3.20 (s, 3H), 3.30 (m, 2H), 4.10 (s, 3H), 7.45 (t, 1H), 7.80 (d, 2H), 8.00 (d, 2H), 8.75 (s, 1H), 10.70 (s, 1H)	377	Meth 27	Meth 40

24	2-{4-[N-(2-Methoxyethyl)sulphamoyl]anilino}-4-butoxy-5-cyanopyrimidine	0.90 (t, 3H), 1.40 (m, 2H), 1.75 (m, 2H), 2.85 (q, 2H), 3.15 (s, 3H), 3.30 (t, 2H), 4.45 (t, 2H), 7.50 (t, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.70 (s, 1H)	405	Meth 28	Meth 38
25	2-{4-[N-(3-Methoxypropyl)sulphamoyl]anilino}-4-butylthio-5-cyanopyrimidine	0.85 (t, 3H), 1.40 (m, 2H), 1.55 (m, 2H), 1.65 (m, 2H), 2.75 (q, 2H), 3.10 (s, 3H), 3.30 (m, 4H), 7.40 (t, 1H), 7.70 (d, 1H), 7.90 (d, 1H), 8.65 (s, 1H)	435	Meth 32	Meth 40
26	2-{4-[N-(2-Methoxyethyl)sulphamoyl]anilino}-4-butylthio-5-cyanopyrimidine	0.90 (t, 3H), 1.40 (m, 2H), 1.65 (m, 2H), 2.90 (q, 2H), 3.10 (s, 3H), 3.30 (m, 4H), 7.55 (t, 1H), 7.70 (d, 2H), 7.90 (d, 2H), 8.60 (s, 1H)	421	Meth 32	Meth 38
27	2-{4-[N-(Tetrahydrofur-2-ylmethyl)sulphamoyl]anilino}-4-(2-propyn-1-yloxy)-5-cyanopyrimidine	1.50 (m, 1H), 1.70-1.90 (br m, 3H), 2.75 (t, 2H), 3.55 (m, 1H), 3.65 (m, 1H), 3.70 (m, 1H), 3.80 (m, 1H), 5.20 (d, 2H), 7.55 (t, 1H), 7.55 (d, 2H), 7.95 (d, 2H), 8.80 (s, 1H)	413	Meth 17	Meth 39
28	2-{4-[N-(Cyclopropyl)sulphamoyl]anilino}-4-(2-propyn-1-yloxy)-5-cyanopyrimidine	0.40 (m, 2H), 0.50 (m, 2H), 2.10 (m, 1H), 3.70 (s, 1H), 5.10 (d, 2H), 7.60 (m, 3H), 7.95 (d, 2H), 8.45 (s, 1H)	369	Meth 17	Meth 41
29	2-[4-(N,N-Dimethylsulphamoyl)anilino]-4-(2-propyn-1-yloxy)-5-cyanopyrimidine	2.60 (s, 6H), 3.70 (s, 1H), 5.20 (d, 2H), 7.70 (d, 2H), 8.00 (d, 2H), 8.80 (s, 1H)	357	Meth 17	Com av



30	2-(4-Sulphamoyl anilino)-4-(2-propyn-1-yloxy)-5-cyano pyrimidine	3.70 (s, 1H), 5.15 (s, 2H), 7.20 (s, 2H), 7.75 (d, 2H), 7.90 (d, 2H), 8.80 (s, 1H)	329	Meth 17	Com av
31	2-(4-Ethylsulphonyl anilino)-4-isopropoxy-5-cyanopyrimidine	1.10 (t, 3H), 1.35 (d, 6H), 3.23 (q, 2H), 5.45 (m, 1H), 7.83 (d, 2H), 7.95 (d, 2H), 8.70 (s, 1H)	346	Meth 26	Ref 1
32	2-[4-( <i>N</i> -Methyl sulphamoyl)anilino]-4-(2-propyn-1-yloxy)-5-cyanopyrimidine	2.40 (d, 3H), 3.70 (m, 1H), 5.20 (m, 2H), 7.28 (q, 1H), 7.72 (d, 2H), 7.95 (d, 2H), 8.80 (s, 1H)	343	Meth 17	Ref 2
33	2-{4-[ <i>N</i> -Methyl- <i>N</i> -(2-methoxyethyl) sulphamoyl]anilino}-4-(2-propyn-1-yloxy)-5-cyano pyrimidine	2.70 (s, 3H), 3.10 (t, 2H), 3.20 (s, 3H), 3.43 (t, 2H), 3.73 (m, 1H), 5.18 (s, 2H), 7.74 (d, 2H), 8.00 (d, 2H), 8.80 (s, 1H)	401	Meth 17	Ref 3
34	2-[4-( <i>N</i> -Cyclobutyl sulphamoyl)anilino]-4-(2-propyn-1-yloxy)-5-cyanopyrimidine	1.45 (m, 2H), 1.70 (m, 2H), 1.90 (m, 2H), 3.60 (m, 1H), 3.70 (m, 1H), 5.17 (m, 2H), 7.70 (d, 2H), 7.80 (d, 1H), 7.90 (d, 2H), 8.80 (s, 1H)	483	Meth 17	Meth 54
35	2-{4-[ <i>N</i> -(Cyclopropyl methyl)sulphamoyl] anilino}-4-(2-propyn-1-yloxy)-5-cyanopyrimidine	0.10 (m, 2H), 0.40 (m, 2H), 0.83 (m, 1H), 2.68 (t, 2H), 3.75 (t, 1H), 5.20 (d, 2H), 7.60 (t, 1H), 7.80 (d, 2H), 7.95 (d, 2H), 8.83 (s, 1H)	383	Meth 17	Meth 55
36	2-{4-[ <i>N</i> -(3-Methoxy propyl)sulphamoyl] anilino}-4-(but-2-yloxy)-5-cyanopyrimidine	0.95 (t, 3H), 1.35 (d, 3H), 1.58 (m, 2H), 1.72 (m, 2H), 2.75 (q, 2H), 3.15 (s, 3H), 3.25 (t, 2H), 5.25 (m, 1H), 7.40 (t, 1H), 7.72 (d, 2H), 7.90 (d, 2H), 8.70 (s, 1H)	419	Meth 16	Ref 4

Ref 1: Helv. Chim. Acta, 66(4), 1046-52, (1983)

Ref 2: J.Med.Chem, 40(11), 1619-1633, (1997)

Ref 3 Method 16 WO 02/ 04429

Ref 4 Method 4 WO 02/ 04429

5

#### Example 37

##### 2-{4-[N-(2-Piperidinoethyl)sulphamoyl]anilino}-4-isopropoxy-5-cyanopyrimidine

To a stirred suspension of 2-chloro-4-isopropoxy-5-cyanopyrimidine (Method 26; 505mg, 2.56mmol) and 4-[N-(2-piperidinoethyl)sulphamoyl]aniline (Method 43; 362mg, 1.28 mmol) in 2-butanol (10ml) was added 1M HCl in ether (3.6ml, 3.6 mmol). The reaction was warmed to 70°C and stirred for 18 hours. The reaction was filtered and the solvent removed under reduced pressure to yield a yellow solid. This solid was partitioned between DCM (40ml) and 2M sodium hydroxide (40ml). The phases were separated and the aqueous layer was extracted with DCM (30ml). The organic phases were combined and washed with water (30ml) and brine (30ml). Solvent was removed under reduced pressure and the resulting solid was recrystallized from methanol to give the title compound (15mg). NMR: 1.35 (m, 2H), 1.45 (m, 10H), 2.25 (m, 6H), 2.85 (m, 2H), 5.45 (m, 1H), 7.30 (br s, 1H), 7.80 (d, 2H), 7.90 (d, 2H), 8.75 (s, 1H), 10.60 (br s, 1 H); m/z 444.

#### 20 Example 38

##### 2-{4-[N-(2,2,2-Trifluoroethyl)sulphamoyl]anilino}-4-(2-methoxyethoxy)-5-cyanopyrimidine

To a solution of 2-{4-[N-(2,2,2-trifluoroethyl)sulphamoyl]anilino}-4-(4-chlorophenoxy)-5-cyanopyrimidine (Method 35; 386mg, 0.8mmol) in 2-methoxyethanol (6ml) was added 1M HCl in ether (1.6ml, 1.6mmol). The reaction was stirred at 115°C for 48 hours. Solvent was removed under reduced pressure and the product recrystallised from methanol to give the title compound (152mg). NMR: 3.30 (s, 3H), 3.60-3.80 (m, 4H), 4.60 (t, 2H), 7.80 (d, 2H), 7.90 (d, 2H), 8.45 (t, 1H), 8.75 (s, 1H); m/z 431.

#### Examples 39-40

30 The following compounds were prepared using the procedure of Example 38 and the appropriate starting material.

Ex	Compound Name	NMR	m/z	SM
39	2-{4-[N-(2-Methoxyethyl) sulphamoyl]anilino}-4-(2-methoxyethoxy)-5-cyanopyrimidine	2.85 (q, 2H), 3.15 (s, 3H), 3.25 (m, 5H), 3.70 (m, 2H), 4.60 (m, 2H), 7.50 (t, 1H), 7.75 (d, 2H), 7.90 (d, 2H), 8.75 (s, 1H)	407	Meth 37
40	2-(4-ethylsulphonyl anilino)-4-(2-methoxy ethoxy)-5-cyanopyrimidine	1.10 (t, 3H), 3.20-3.40 (m, 5H), 3.75 (d, 2H), 4.65 (d, 2H), 7.85 (d, 2H), 8.00 (d, 2H), 8.80 (s, 1H), 10.80 (br s, 1H)	362	Meth 36

### Preparation of Starting Materials

The starting materials for the above Examples are either commercially available or are readily prepared by standard methods from known materials. For example the following reactions are illustrations but not limitations of the preparation of some of the starting materials used in the above reactions.

#### Method 1

##### 10 2-Chloro-4-(2-propyn-1-yloxy)-5-N-*t*-butylcarbamoylpyrimidine

Sodium hydride (60% suspension in mineral oil, 720mg, 0.018mol) was added to a solution of propargyl alcohol (0.70ml, 0.012mol) in dry THF (70ml). When effervescence had stopped the resulting suspension was slowly added to a solution of 5-N-*t*-butylcarbamoyl-2,4-dichloropyrimidine (Method 51; 3.00g, 0.012mol) in dry THF (130ml). The reaction was stirred at room temperature for 18 hours. Solvent was removed under reduced pressure and the resulting solid was triturated with ether (50ml). The suspension was filtered and the ether filtrate was washed with citric acid (25ml), water (25ml) and brine (25ml) then dried. Removal of solvent gave the title compound (3.09g, 96%). NMR: 1.30 (s, 10H), 3.70 (m, 1H), 5.10 (d, 2H), 7.80 (br s, 1H), 8.65 (s, 1H); m/z 268

20

#### Methods 2-16

Using the procedure of method 1 and using the appropriate alcohols, or thiols the following compounds were prepared. (N.B. Method 5 was used without purification).

Meth	Compound Name	m/z
2	2-Chloro-4-(tetrahydrofur-3-yloxy)-5- <i>N-t</i> -butylcarbamoylpyrimidine	299
3	2-Chloro-4-(tetrahydrofur-3-ylmethoxy)-5- <i>N-t</i> -butylcarbamoylpyrimidine	313
4	2-Chloro-4-(2-butyln-1-yloxy)-5- <i>N-t</i> -butylcarbamoylpyrimidine	281
5	2-Chloro-4-(3-butyln-1-yloxy)-5- <i>N-t</i> -butylcarbamoylpyrimidine	
6	2-Chloro-4-(2-methoxyethoxy)-5- <i>N-t</i> -butylcarbamoylpyrimidine	287

Meth	Compound Name	NMR	m/z
7	2-Chloro-4-(3-butyln-2-yloxy)-5- <i>N-t</i> -butylcarbamoylpyrimidine	1.35 (s, 9H), 1.60 (m, 3H), 3.65 (s, 1H), 5.70 (m, 1H), 7.70 (m, 1H), 8.65 (s, 1H)	281
8	2-Chloro-4-(2-morpholinoethoxy)-5- <i>N-t</i> -butylcarbamoylpyrimidine	1.35 (s, 9H), 2.45 (m, 4H), 2.70 (t, 2H), 3.55 (m, 4H), 4.50 (t, 2H), 7.75 (br s, 1H), 8.65 (s, 1H)	342
9	2-Chloro-4-[2-(2-methoxyethoxy)ethoxy]-5- <i>N-t</i> -butylcarbamoylpyrimidine	1.35 (s, 9H), 3.20 (s, 3H), 3.45 (m, 2H), 3.55 (m, 2H), 3.80 (m, 2H), 4.50 (m, 2H), 7.70 (br s, 1H), 8.70 (s, 1H)	331
10	2-Chloro-4-(cyclopropylmethoxy)-5- <i>N-t</i> -butylcarbamoylpyrimidine	0.45 (m, 2H), 0.65 (m, 2H), 1.30 (m, 1H), 1.40 (s, 9H), 4.30 (d, 2H), 7.80 (br s, 1H), 8.40 (s, 1H)	283
11	2-Chloro-4-ethoxy-5- <i>N-t</i> -butylcarbamoylpyrimidine	1.35 (m, 12H), 4.45 (q, 2H), 7.75 (br s, 1H), 8.60 (s, 1H)	257
12	2-Chloro-4-isopropoxy-5- <i>N-t</i> -butylcarbamoylpyrimidine	1.35 (m, 15H), 5.30 (m, 1H), 7.65 (br s, 1H), 8.60 (s, 1H)	271
13	2-Chloro-4-methoxy-5- <i>N-t</i> -butylcarbamoylpyrimidine	1.35 (s, 9H), 4.00 (s, 3H), 7.75 (br s, 1H), 8.60 (s, 1H)	
14	2-Chloro-4-butoxy-5- <i>N-t</i> -butylcarbamoylpyrimidine	0.90 (t, 3H), 1.35 (s, 9H), 1.45 (m, 2H), 1.70 (m, 2H), 4.40 (t, 2H), 7.75 (br s, 1H), 8.60 (s, 1H)	285
15	2-Chloro-4-butylthio-5- <i>N-t</i> -butylcarbamoylpyrimidine	0.90 (t, 3H), 1.30-1.45 (br m, 11H), 1.60 (m, 2H), 3.10 (t, 2H), 8.15 (br s, 1H), 8.40 (s, 1H)	301

16	2-Chloro-4-but-2-yloxy-5- <i>N</i> - <i>t</i> -butylcarbamoylpyrimidine	0.83 (t, 3H), 1.32 (m, 12H), 1.70 (m, 2H), 5.20 (m, 1H), 7.70 (br s, 1H), 8.60 (s, 1H)	285
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**Method 17****2-Chloro-4-(2-propyn-1-yloxy)-5-cyanopyrimidine**

A solution of 2-chloro-4-(2-propyn-1-yloxy)-5-*N*-*t*-butylcarbamoylpyrimidine (Method 1; 3.49g, 0.013mol) in thionyl chloride (135ml) was heated at 95°C for 18 hours. Solvent was removed under reduced pressure and the resulting brown oil dissolved in ether. Ether was removed under reduced pressure to give the title compound as an oil (3g) which was used crude in subsequent reactions. NMR: 3.75 (t, 1H), 5.15 (d, 2H), 5.45 (br s, 2H), 9.05 (s, 1H); *m/z* 193.

10

**Methods 18-32**

Using the procedure of Method 17 the following compounds were prepared. In most cases purity was checked by HPLC and the product was used crude in the next reaction.

Meth	Compound Name	SM
18	2-Chloro-4-(tetrahydrofur-3-yloxy)-5-cyanopyrimidine	Meth 2
19	2-Chloro-4-(tetrahydrofur-3-ylmethoxy)-5-cyanopyrimidine	Meth 3
20	2-Chloro-4-(2-butyn-1-yloxy)-5-cyanopyrimidine	Meth 4
21	2-Chloro-4-(3-butyn-1-yloxy)-5-cyanopyrimidine	Meth 5
22	2-Chloro-4-(2-methoxyethoxy)-5-cyanopyrimidine	Meth 6
23	2-Chloro-4-(3-butyn-2-yloxy)-5-cyanopyrimidine	Meth 7
24	2-Chloro-4-(2-morpholinoethoxy)-5-cyanopyrimidine	Meth 8
25	2-Chloro-4-(cyclopropylmethoxy)-5-cyanopyrimidine	Meth 10
26	2-Chloro-4-isopropoxy-5-cyanopyrimidine	Meth 12
27	2-Chloro-4-methoxy-5-cyanopyrimidine	Meth 13
28	2-Chloro-4-butoxy-5-cyanopyrimidine	Meth 14
29	2-Chloro-4-but-2-yloxy-5-cyanopyrimidine	Meth 16

Meth	Compound Name	<i>m/z</i>	SM
30	2-Chloro-4-[2-(2-methoxyethoxy)ethoxy]-5-cyanopyrimidine	257	Meth 9

15

Meth	Compound Name	NMR	SM
31	2-Chloro-4-ethoxy-5-cyanopyrimidine	1.35 (t, 3H), 4.50 (q, 2H), 9.00 (s, 1H)	Method 11
32	2-Chloro-4-butylthio-5-cyanopyrimidine	0.90 (t, 3H), 1.40 (m, 3H), 1.65 (m, 3H), 3.25 (t, 2H), 8.90 (s, 1H)	Method 15

**Method 33****2-Chloro-4-(4-chlorophenoxy)-5-*N*-*t*-butylcarbamoylpyrimidine**

To a solution of 4-chlorophenol (338mg, 2.63mmol) in dry THF (10ml) was added sodium hydride (105mg, 2.63mmol). When effervescence had stopped this solution was slowly added to a solution of 2,4-dichloro-5-*N*-*t*-butylcarbamoylpyrimidine (Method 51; 680mg, 2.74 mmol) in dry THF (15ml). The reaction was stirred at room temperature for 2 hours. Solvent was removed under reduced pressure and the resulting solid was suspended in diethyl ether (50ml). The solid was filtered and the filtrate was washed with 2M sodium hydroxide (30ml), citric acid (30ml), water (30ml) and brine (30ml) before drying. Removal of the ether gave the title compound (880mg, 99%). *M/z* 339.

**Method 34****2-Chloro-4-(4-chlorophenoxy)-5-cyanopyrimidine**

A solution of 2-chloro-4-(4-chlorophenoxy)-5-*N*-*t*-butylcarbamoylpyrimidine (Method 33; 200mg, 0.59mmol) in thionyl chloride (5ml, 69mmol) was heated at 95°C for 18 hours. The thionyl chloride was removed under reduced pressure and the resulting brown oil was dissolved in diethyl ether (25ml). The ether was removed under reduced pressure to give the title compound (210mg). NMR: 7.35 (d, 2H), 7.55 (d, 2H), 9.20 (s, 1H).

**Method 35****2-{4-[*N*-(2,2,2-Trifluoroethyl)sulphamoyl]anilino}-4-(4-chlorophenoxy)-5-cyanopyrimidine**

A suspension of 2-chloro-4-(4-chlorophenoxy)-5-cyanopyrimidine (Method 34; 500mg, 1.88mmol) and 4-[*N*-(2,2,2-trifluoroethyl)sulphamoyl]aniline (Method 44; 432mg, 1.70mmol) in 2-butanol (10ml) was stirred at 45°C for 18 hours. Solvent was removed under reduced pressure and the product triturated with ether. The resulting solid was collected by

filtration and washed with ether to give the title compound (480mg) which was used crude in subsequent reactions. M/z 483.

### Methods 36-37

- 5 Following the procedure of method 35 and using the appropriate aniline starting material the following compounds were prepared.

Meth	Compound Name	m/z
36	2-(4-Ethylsulphonylanilino)-4-(4-chlorophenoxy)-5-cyanopyrimidine	414
37 <sup>1</sup>	2-{4-[N-(2-Methoxyethyl)sulphamoyl]anilino}-4-(4-chlorophenoxy)-5-cyanopyrimidine	459

<sup>1</sup> Aniline: Method 38.

### Method 38

#### 10 4-[N-(2-Methoxyethyl)sulphamoyl]aniline

A mixture of 2-methoxyethylamine (859mg, 11.4mmol), sulphanilyl fluoride (1.0g, 5.71mmol) and triethylamine (1.72g, 22.9mmol) in 1-butanol (15ml) was heated at reflux for 18 hours. The mixture was allowed to cool and the volatiles were removed by evaporation. The residue was purified by chromatography eluting with ethyl acetate / hexane (50:50)

- 15 increasing in polarity to (70:30) to give the title compound (860mg, 65%). NMR: 2.78 (q, 2H), 3.15 (s, 3H), 3.25 (t, 2H), 5.87 (s, 2H), 6.58 (d, 2H), 7.10 (t, 1H), 7.40 (d, 2H); m/z 231.

### Method 39-44

The following compounds were prepared using the procedure of Method 38.

Meth	Compound Name	m/z
39	4-[N-(Tetrahydrofur-2-ylmethyl)sulphamoyl]aniline	257

20

Meth	Compound Name	NMR	m/z
40	4-[N-(3-Methoxypropyl)sulphamoyl]aniline	1.60 (m, 2H), 2.95 (q, 2H), 3.20 (s, 3H), 3.30 (t, 2H), 4.10 (br s, 2H), 4.90 (br t, 1H), 6.60 (d, 2H), 7.55 (d, 2H)	244
41	4-(N-Cyclopropylsulphamoyl)aniline	0.01-0.15 (m, 4H), 1.70-1.75 (m, 1H), 5.60 (s, 2H), 6.30 (d, 2H), 7.05 (s, 1H), 7.10 (d, 2H)	230

42	4-( <i>N</i> -Allylsulphamoyl) aniline	3.30 (t, 2H), 5.00 (d, 1H), 5.10 (d, 1H), 5.65 (m, 1H), 5.85 (s, 2H), 6.40 (d, 2H), 7.20 (t, 1H), 7.40 (d, 2H)	212
43	4-[ <i>N</i> -(2-Piperidinoethyl) sulphamoyl]aniline	1.30 (br m, 2H), 1.40 (br m, 4H), 2.25 (br m, 6H), 2.70 (br t, 2H), 5.85 (s, 2H), 6.60 (d, 2H), 6.80 (br s, 1H), 7.40 (d, 2H)	283
44	4-[ <i>N</i> -(2,2,2- Trifluoroethyl) sulphamoyl]aniline	3.50 (m, 2H), 5.90 (br s, 2H), 6.60 (d, 2H), 7.40 (d, 2H), 8.00 (br t, 1H)	254

**Method 45**1-Nitro-4-[4-(phthalimido)butylsulphide]phenyl

4-Nitrothiophenol (1.9g, 12.26 mmol) was stirred in DMF under nitrogen and cooled (ice/water bath). Sodium hydride (60% dispersion in oil: 400mg, 10mmol) was added in portions and the mixture stirred for 10 minutes. *N*-(4-bromobutyl)phthalimide (2.8g, 9.93 mmol) in DMF (10ml) was added and the reaction was heated at 90°C for 1.5 hours, cooled to room temperature and stood overnight at ambient temperature. Volatiles were removed by evaporation, water (20ml) was added and the solution was extracted into ethyl acetate (50 + 25 ml). The organic layers were combined, washed with water (20ml) and brine (20 ml), dried and the volatiles evaporated. The resulting gum was triturated twice with isohexane. The solvent was decanted to give the title compound as a solid (3.8g). NMR: 1.64 (m, 2H), 1.74 (m, 2H), 3.12 (t, 2H), 3.60 (t, 2H), 7.45 (d, 2H), 7.81 (m, 4H), 8.06 (d, 2H)

**Method 46**1-Nitro-4-[4-(phthalimido)butylsulphonyl]phenyl

A solution of chromium(VI)oxide (3.5g, 35.0 mmol) in water (3ml) and glacial acetic acid (12.5 ml) was added dropwise over 15 to 20 minutes to a solution of 1-nitro-4-[4-(phthalimido)butylsulphide]phenyl (Method 45; 3.5g, 9.83 mmol) in glacial acetic acid (17.5ml) heated at 90-100°C. The mixture was then heated at 100°C for 3.5 hours. The reaction was cooled, poured onto crushed ice (250g), and the solid was collected by filtration and washed with water. The solid was dried by azeotroping with methanol 3 times to give the title compound (3.4g). m/z 389.



**Method 47****1-Nitro-4-(4-aminobutylsulphonyl)phenyl**

1-Nitro-4-[4-(phthalimido)butylsulphonyl]phenyl (Method 46; 3g, 7.73 mmol) was heated at 90°C in acetonitrile (30ml) and methanol (10ml). Hydrazine hydrate (0.76ml, 15.7 mmol) was added and the reaction was heated for 1.5 hours, then cooled, and stood overnight at ambient temperature. The resulting solid was removed by filtration and washed with methanol. The combined filtrates were evaporated to give the title compound (2.3g). m/z 259.

**Method 48**10 **1-Nitro-4-[4-(isopropylamino)butylsulphonyl]phenyl**

1-Nitro-4-(4-aminobutylsulphonyl)phenyl (Method 47; 2g, 7.75mmol) was stirred in methanol (20ml) and acetone (2.3ml) was added. Sodium cyanoborohydride (730mg, 11.62mmol) was added in portions over 5 minutes and the reaction was stirred for 2.5 hours. Water (15ml) was added, and the organic solvents were removed by evaporation. Water (20ml) was added and the solution was extracted with ethyl acetate (2x60ml). The combined organic layers were washed with water (25ml) and brine (25ml). The volatiles were evaporated and the residue was purified by chromatography on neutral alumina (activity II), eluting with DCM increasing polarity to methanol : DCM (3:97) to give the title compound (1.26g). m/z 301

20

**Method 49****4-[4-(Isopropylamino)butylsulphonyl]aniline**

1-Nitro-4-[4-(isopropylamino)butylsulphonyl]phenyl (Method 48; 1.2g, 4mmol) was dissolved in ethanol (20ml) and 1M hydrochloric acid and hydrogenated at 1 atmosphere over 10% palladium on carbon for 4 hours. The catalyst was removed by filtration and the volatiles evaporated to give the title compound as a foam. m/z 271.

**Method 50****2,4-Dichloro-5-chloroformylpyrimidine**

30 5-Carboxy-2,4-dihydropyrimidine (19.0g, 0.12mol), phosphorous pentachloride (83.5g, 0.40mol); and phosphoryl chloride (28.3ml, 0.30mol) were heated at 114°C for 5 hours. The resulting solution was cooled overnight and the volatiles removed by evaporation.

The residue was purified by vacuum distillation to yield the title compound as a clear oil (17.85g, 70%). M/z 211.

### Method 51

#### 5 2,4-Dichloro-5-*N*-*t*-butylcarbamoylpyrimidine

A solution of 2,4-dichloro-5-chloroformylpyrimidine (Method 50; 9.8g, 46.3mmol) in dry THF (50ml) was cooled to -15°C. *t*-Butylamine (5.2ml, 49.3mmol) and triethylamine (6.9ml, 49.5mmol) in dry THF (20ml) were added slowly so as to maintain the temperature below -10°C. The resulting mixture was stirred at -10°C for 2 hours, allowed to warm to ambient temperature and stirred for a further 30 minutes. The precipitate was removed by filtration and the filtrate evaporated to give a viscous oil. High vacuum evaporation gave a solid (10.48 g, 90%). NMR: 1.49 (s, 9H), 6.19 (brs, 1H), 8.86 (s, 1H); m/z 248.

### Method 52

#### 15 4-(*N*-Cyclobutylsulphamoyl)nitrobenzene

A stirred solution of triethylamine (7.8ml, 0.056mol) and cyclobutylamine (4.8ml, 0.056mol) in DCM (100ml) was cooled in an ice/water bath. A solution of 4-nitrobenzene sulphonyl chloride (11.3g, 0.051mol) in DCM (100ml) was added dropwise. The reaction was stirred for one hour the cooling bath was removed and the mixture stirred for further 3 hours. The reaction mixture was washed with 1M hydrochloric acid (80ml), water (50ml) and then brine. The volatiles were evaporated to give the title compound (11.79g). NMR: 1.50 (m, 2H), 1.75 (m, 2H), 1.9 (m, 2H), 3.70 (m, 1H), 8.00 (d, 2H), 8.30 (d, 1H), 8.40 (d, 2H); m/z: 256.

### Method 53

25 Using the procedure of Method 52 starting from 4-nitrobenzenesulphonyl chloride and the appropriate commercially available amine the following compounds were prepared.

Meth	Compound Name	NMR	m/z
53	4-[ <i>N</i> -(Cyclopropylmethyl) sulphamoyl]nitrobenzene	0.10 (m, 2H), 0.35 (m, 2H), 0.83 (m, 1H), 2.75 (t, 2H), 8.05 (d, 2H), 8.13 (m, 1H), 8.45 (d, 2H)	256

**Method 54****4-(N-Cyclobutylsulphamoyl)aniline**

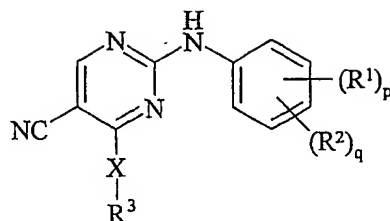
4-(N-Cyclobutylsulphamoyl)nitrobenzene (Method 52; 11.79g) was reduced by hydrogenation in ethanol (300ml) over 10% palladium on carbon (1g) at 3 bar pressure. The catalyst was removed by filtration and the volatiles evaporated to give the title compound (7.84g). NMR: 1.50 (m, 2H), 1.75 (m, 2H), 1.93 (m, 2H), 3.60 (m, 1H), 5.90 (br s, 2H), 6.65 (d, 2H), 7.45 (d, 2H); m/z: 226.

**Method 55**10 **4-[N-(Cyclopropylmethyl)sulphamoyl]aniline**

4-[N-(Cyclopropylmethyl)sulphamoyl]nitrobenzene (Method 53; 12.58g) was reduced by hydrogenation in ethanol (300ml) over 10% palladium on carbon (1g) at 3 bar pressure. The catalyst was removed by filtration and the volatiles evaporated. 2g of this crude product was purified by chromatography eluting with DCM increasing in polarity to 10% MeOH/DCM to give the title compound (850mg). NMR: 0.08 (m, 2H), 0.25 (m, 2H), 0.83 (m, 1H), 2.80 (t, 2H), 4.15 (br s, 2H), 4.50 (br t, 1H), 6.65 (d, 2H), 7.62 (d, 2H); m/z: 226.

**Claims**

1. A compound of formula (I):



(I)

wherein:

X is -O- or -S-;

R¹ is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, C₁-₆alkyl, C₂-₆alkenyl and C₂-₆alkynyl;

p is 0-4; wherein the values of R¹ may be the same or different;

R² is selected from sulphonyl and a group R⁴-E-;

q is 0-2; wherein the values of R² may be the same or different; and wherein p + q = 1-5;

R³ is selected from C₁-₆alkyl, C₂-₆alkenyl, C₂-₆alkynyl, C₃-₈cycloalkyl and heterocyclyl;

wherein R³ may be optionally substituted by one or more R⁵; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R⁶; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R⁷;

R⁴ is selected from C₁-₆alkyl, C₂-₆alkenyl, C₂-₆alkynyl, C₃-₈cycloalkyl,

C₃-₈cycloalkylC₁-₆alkyl, phenyl, a heterocyclic group, phenylC₁-₆alkyl and (heterocyclic group)C₁-₆alkyl; wherein R⁴ may be optionally substituted on carbon by one or more R⁸; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R⁹;

E is selected from -C(O)-, -N(R⁸)C(O)-, -C(O)N(R⁸)-, -S(O)ᵣ-, -SO₂N(R⁸)- and

-N(R⁸)SO₂-; wherein R⁸ is hydrogen or C₁-₆alkyl optionally substituted by one or more R¹⁰ and r is 1-2;

R⁵ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphonyl, C₁-₆alkyl, C₂-₆alkenyl, C₂-₆alkynyl, C₁-₆alkoxy,

C<sub>1-6</sub>alkanoyl, C<sub>1-6</sub>alkanoyloxy, *N*-(C<sub>1-6</sub>alkyl)amino, *N,N*-(C<sub>1-6</sub>alkyl)<sub>2</sub>amino, C<sub>1-6</sub>alkanoylamino, *N*-(C<sub>1-6</sub>alkyl)carbamoyl, *N,N*-(C<sub>1-6</sub>alkyl)<sub>2</sub>carbamoyl, C<sub>1-6</sub>alkylS(O)<sub>a</sub>, wherein a is 0 to 2, C<sub>1-6</sub>alkoxycarbonyl, *N*-(C<sub>1-6</sub>alkyl)sulphamoyl, *N,N*-(C<sub>1-6</sub>alkyl)<sub>2</sub>sulphamoyl, C<sub>3-8</sub>cycloalkyl, phenyl and a heterocyclic group; wherein R<sup>5</sup> may be optionally substituted on carbon by one or more R<sup>11</sup>; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R<sup>12</sup>;

R<sup>6</sup>, R<sup>7</sup>, R<sup>9</sup> and R<sup>12</sup> are independently selected from C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkylsulphonyl, C<sub>1-4</sub>alkoxycarbonyl, carbamoyl, *N*-(C<sub>1-4</sub>alkyl)carbamoyl, *N,N*-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; wherein R<sup>6</sup>, R<sup>7</sup>, R<sup>9</sup> and R<sup>12</sup> may be independently optionally substituted on carbon by one or more R<sup>13</sup>;

R<sup>8</sup> and R<sup>10</sup> are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkanoyl, C<sub>1-6</sub>alkanoyloxy, *N*-(C<sub>1-6</sub>alkyl)amino, *N,N*-(C<sub>1-6</sub>alkyl)<sub>2</sub>amino, C<sub>1-6</sub>alkanoylamino, *N*-(C<sub>1-6</sub>alkyl)carbamoyl, *N,N*-(C<sub>1-6</sub>alkyl)<sub>2</sub>carbamoyl, C<sub>1-6</sub>alkylS(O)<sub>a</sub> wherein a is 0 to 2, C<sub>1-6</sub>alkoxycarbonyl, *N*-(C<sub>1-6</sub>alkyl)sulphamoyl and *N,N*-(C<sub>1-6</sub>alkyl)<sub>2</sub>sulphamoyl; wherein R<sup>8</sup> and R<sup>10</sup> may be independently optionally substituted on carbon by one or more R<sup>14</sup>; and

R<sup>11</sup>, R<sup>13</sup> and R<sup>14</sup> are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxyl, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphanyl, ethylsulphanyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl; or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

2. A compound of formula (I) as claimed in claim 1, wherein X is -O- or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

30

3. A compound of formula (I) as claimed in claim 1, wherein X is -S- or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

4. A compound of formula (I) as claimed in any one of claims 1 - 3 wherein  $R^1$  is halo or  $C_{1-2}$ alkyl or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.
- 5 5. A compound of formula (I) as claimed in any one of claims 1 - 4 wherein p is 0-2; wherein the values of  $R^1$  may be the same or different or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.
6. A compound of formula (I) as claimed in any one of claims 1 - 5 wherein:
- 10  $R^2$  is sulphonyl or a group  $R^4-E$ ; wherein:
- $R^4$  is selected from  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{3-8}$ cycloalkyl,  $C_{3-8}$ cycloalkyl $C_{1-6}$ alkyl, and (heterocyclic group) $C_{1-6}$ alkyl; wherein  $R^4$  may be optionally substituted on carbon by one or more  $R^8$ ;
- E is selected from  $-S(O)_r-$  and  $-N(R^a)SO_2-$ ; wherein  $R^a$  is hydrogen or  $C_{1-6}$ alkyl and r is
- 15 2; and
- $R^8$  is selected from halo,  $C_{1-6}$ alkoxy and *N*-( $C_{1-6}$ alkyl)amino; or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.
7. A compound of formula (I) as claimed in any one of claims 1 - 6 wherein q is 1 or a
- 20 pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.
8. A compound of formula (I) as claimed in any one of claims 1 - 7 wherein  $R^3$  is selected from  $C_{1-6}$ alkyl,  $C_{2-6}$ alkynyl and heterocyclyl; wherein  $R^3$  may be optionally substituted by one or more  $R^5$ ; wherein:
- 25  $R^5$  is selected from  $C_{1-6}$ alkoxy,  $C_{3-8}$ cycloalkyl and a heterocyclic group; wherein  $R^5$  may be optionally substituted on carbon by one or more  $R^{11}$ ; and
- $R^{11}$  is methoxy; or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.
- 30 9. A compound of formula (I) as depicted in claim 1 wherein:
- X is  $-O-$  or  $-S-$ ;
- p is 0;

$R^2$  is sulphonyl or a group  $R^4$ -E-; wherein:

$R^4$  is selected from  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{3-8}$ cycloalkyl,  $C_{3-8}$ cycloalkyl $C_{1-6}$ alkyl, and (heterocyclic group) $C_{1-6}$ alkyl; wherein  $R^4$  may be optionally substituted on carbon by one or more  $R^8$ ;

5 E is selected from  $-S(O)_r-$  and  $-N(R^a)SO_2-$ ; wherein  $R^a$  is hydrogen or  $C_{1-6}$ alkyl and r is 2;

$R^8$  is selected from halo,  $C_{1-6}$ alkoxy and  $N-(C_{1-6}$ alkyl)amino;

q is 1;

$R^3$  is selected from  $C_{1-6}$ alkyl,  $C_{2-6}$ alkynyl and heterocyclyl; wherein  $R^3$  may be  
10 optionally substituted by one or more  $R^5$ ; wherein:

$R^5$  is selected from  $C_{1-6}$ alkoxy,  $C_{3-8}$ cycloalkyl and a heterocyclic group; wherein  $R^5$  may be optionally substituted on carbon by one or more  $R^{11}$ ; and

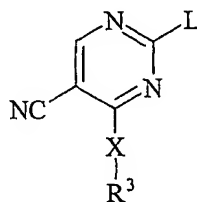
$R^{11}$  is methoxy;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

15

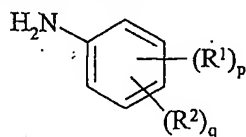
10. A process for preparing a compound of formula (I), as claimed in any one of claims 1-9, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof which process (wherein  $R^1$ ,  $R^2$ ,  $R^3$ , p and q are, unless otherwise specified, as defined in any one of claims 1-9) comprises of:

20 a) reaction of a pyrimidine of formula (II):



(II)

wherein L is a displaceable group; with an aniline of formula (III):

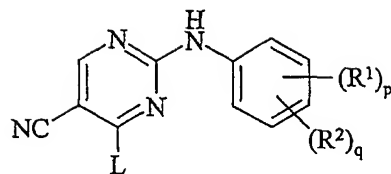


(III)

25

b) reacting a pyrimidine of formula (IV):

- 47 -



(IV)

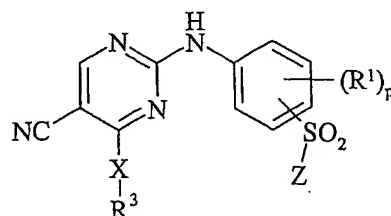
wherein L is a displaceable group; with an compound of formula (V):



(V)

or

c) for compounds of formula (I) where  $R^2$  is sulhamoyl or a group  $R^4-E$  and E is  $-NHSO_2-$ ; reacting a pyrimidine of formula (VI):



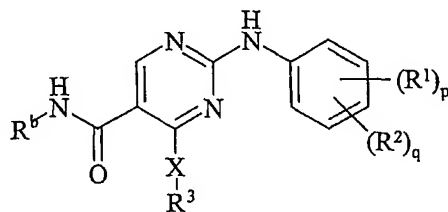
(VI)

wherein Z is a displaceable group; with an amine of formula (VII):



(VII)

d) by converting a compound of formula (VIII):



(VIII)

wherein  $R^b$  is hydrogen or *t*-butyl; into a compound of formula (I);

and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.



11. A pharmaceutical composition which comprises a pyrimidine derivative of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-9, in association with a pharmaceutically-acceptable diluent or carrier.
- 5
12. A compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined in any one of claims 1-9, for use as a medicament.
13. The use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined in any one of claims 1-9, in the manufacture of a medicament for use in the production of a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal such as man.
- 10
14. A method for producing a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as any one of claims 1-9.
- 15

## INTERNATIONAL SEARCH REPORT

national Application No  
PCT/GB 02/02428

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/47 A61K31/505 C07D405/12 C07D413/12 C07D401/12  
A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 50251 A (CALVERT ALAN HILARY ;NOBLE MARTIN EDWARD MANTYLA (GB); BOYLE FRANC) 7 October 1999 (1999-10-07) page 9, line 21 -page 11, line 8 ---	1-14
Y	WO 00 39101 A (BREAULT GLORIA ANNE ;PEASE JANET ELIZABETH (GB); ASTRAZENECA UK LT) 6 July 2000 (2000-07-06) page 2 -page 6, line 12; example 41 ---	1-14
A	WO 00 59892 A (BREAULT GLORIA ANNE ;JAMES STEWART RUSSELL (GB); PEASE JANET ELIZA) 12 October 2000 (2000-10-12) page 1, line 27 -page 4, line 1 ---	1-14
A	EP 0 135 472 A (CIBA GEIGY AG) 27 March 1985 (1985-03-27) page 1, line 9 -page 2, line 16 ---	1-10
-/--		

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

12 August 2002

Date of mailing of the international search report

20/08/2002

Name and mailing address of the ISA

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Usuelli, A

## INTERNATIONAL SEARCH REPORT

national Application No  
PCT/GB 02/02428

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 64653 A (BREault GLORIA ANNE ;PEASE ELIZABETH JANET (GB); ASTRAZENECA UK LT) 7 September 2001 (2001-09-07) page 2 -page 5, line 8 -----	1-14
P,X	WO 01 64654 A (BREault GLORIA ANNE ;PEASE ELIZABETH JANET (GB); ASTRAZENECA UK LT) 7 September 2001 (2001-09-07) page 1, line 24 -page 5, line 14 -----	1-14
P,X	WO 01 64655 A (BREault GLORIA ANNE ;PEASE ELIZABETH JANET (GB); ASTRAZENECA UK LT) 7 September 2001 (2001-09-07) page 2 -page 5, line 16 -----	1-14
P,X	WO 01 64656 A (PEARSON STUART ERIC ;PEASE ELIZABETH JANET (GB); ASTRAZENECA UK LT) 7 September 2001 (2001-09-07) page 1, line 25 -page 5, line 6 -----	1-14

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB 02/02428

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claim 14 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No

PCT/GB 02/02428

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9950251	A	07-10-1999	AU 3155199 A CA 2326357 A1 EP 1066266 A1 WO 9950251 A2 JP 2002509921 T	18-10-1999 07-10-1999 10-01-2001 07-10-1999 02-04-2002
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